II. REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim Amendments

Claims 10, 11, 15, 18, 19, 23, 26, 27, and 31 stand withdrawn as being drawn to non-elected inventions.

Claims 5-9, 12, 16-17, 20, 24-25, 28, 32-33, 36 and 40-55 stand canceled without prejudice or disclaimer.

Claim 4, 34-35, and 37-39 are now canceled without prejudice or disclaimer.

Claims 1 and 2 are amended to delete the recitation of the phrase "from 60-180 μg of." No new matter is added by the amendment.

Entry of the amendment is respectfully requested. The amendments are made in a sincere effort to place the claims in condition for allowance or in better form for consideration on appeal and do not require an additional search of the art. The amendments were not made earlier as it was Applicant's belief that the claims as previously presented defined patentable subject matter.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, Claims 1-3, 13-14, 21-22, 29-30, and 56-58 are pending in this application and are currently under examination.

Information Disclosure Statement (IDS)

Applicants thank the Office for acknowledging the IDS submitted on October 21, 2008.

Claim Rejection under 35 U.S.C. § 103

Claims 1-4, 13-14, 21-22, 29-30, 37-38 and 56-58 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Emtage et al. (*J. Immuno.* 160:2531-38, 1998) in view of Wilson et al. (*Int. J. Radiation Oncology Biol. Phys.*, 42:905-908, 1998), or Lash et al. (*Br. J Cancer.* 78(4):439-45, 1998, abstract).

Before addressing the rejection, Applicants note a few salient features of the claimed invention as follows:

1. Combination of deoxyribonucleic acid (DNA) encoding B7.1 with DMXAA; and

2. Administration of Deoxyribonucleic acid (DNA) encoding B7.1 prior to administering an optimal dose of DMXAA.

Without acquiescing to the proprietary of any rejection, Applicants have amended instant claims to remove the recitation of the phrase "from 60-180 μg of" for DNA encoding B7.1. The amount of from 60-180 μg for DNA encoding B7.1 was recited in error in the last response dated October 21, 2008 because it includes the amount of plasmid DNA as well as the DNA encoding B7.1. However, B7.1 is provided as a mouse B7.1 cDNA (see instant specification as filed, paragraph [0068], lines 6-8) in a pCDM8 expression plasmid (see instant specification as filed, paragraph [0085] lines 5 -10).

A mouse B7.1 cDNA is about 1701 base pairs long (Entrez GI: 111038144, http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=111038144, last accessed February 3, 2009). pCDM8 is a E. coli plasmid vector with 4356 base pairs in length (see, e.g. the Vector DB of Stanford Genomic Resources at Stanford University, http://genome-www.stanford.edu/vectordb/vector_descrip/COMPLETE/PCDM8.SEQ.html, last accessed February 3, 2009). Therefore a B7.1/pCDM8 plasmid is about 6,057 base pairs in length.

Based on its entire nucleotide sequence, the molecular weight of B7.1/pCDM8 is about 4.1×10^6 g/mol. 60-180 μg B7.1/pCDM8 is about $1.46 \times 10^{-11} - 4.39 \times 10^{-11}$ mole which is

about $8.8 \times 10^{12} - 2.64 \times 10^{13}$ copies of plasmid molecules. Since one B7.1/pCDM8 contains one copy of B7.1, the number of copies of B7.1 cDNA is also about $8.8 \times 10^{12} - 2.64 \times 10^{13}$.

Now turning to the Office Action, Applicants contend that the Office has not established a *prima facie* case of obviousness because the references in combination do not teach the individual elements or provide a motivation to combine their individual teachings.

Cited references in combination do not teach all the claim elements

Neither of Emtage et al., Wilson et al. or Lash et al. teach administering deoxyribonucleic acid (DNA) encoding B7.1 in any amount prior to administering an optimal dose of DMXAA.

Emtage et al. teach that an adenovirus constructed to express both the costimulatory molecule B7-1 and human IL-2 genes apparently elicits a potent antitumor response when administered intratumorally. See, e.g., abstract of Emtage et al. Nowhere do Emtage et al. teach a sequential administration of its B7-1 and IL-2. The Office cites Lash et al. to apparently show a combination of DMXAA with 5-hydroxytyptamine (5-HT). Nowhere do Lash et al. teach any significance of a specific order of administration of DMXAA with 5-HT.

Therefore, none of the cited references teach the combination of B7.1 and DMXAA or the sequential administration of any two anti-cancer agents.

No suggestion or motivation in cited references

Assuming *arguendo* that the cited references in combination teach the individual elements of the claims, the art does not provide any reason to a skilled artisan to combine the known elements in the fashion claimed. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727-1737 (2007) reviewed the analysis for determining if an invention is obvious over the teachings of the prior art. In *KSR*, *supra.*, the Supreme Court affirmed the factual analysis set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). The *KSR* Court noted that obviousness cannot be proven merely by showing that the elements of a

claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed." *Id.* at 1741.

Emtage et al. teach a combination of B7-1 expressed in adenoviral expression vector with IL-2; Wilson et al. only teach DMXAA in tumor therapy; and Lash et al. teach a combination of DMXAA with 5-HT. 5-HT is an entirely different drug than deoxyribonucleic acid (DNA) encoding B7.1 to be replaced in combination with DMXAA. DMXAA and 5-HT both are tumor blood flow inhibitors. IL-2 and B7-1 promote antitumor immunity since both are T-cell activators (see, e.g., Emtage et al., page 2531, right hand column). Therefore, both Emtage et al. and Lash et al. teach a combination of agents that have substantially the same mechanism of action. The Office has not persuasively explained why a skilled artisan would have had a reason to replace an adenoviral expression vector expressing IL-2 of Emtage et al., which is a T-cell activator, with DMXAA of Lash et al., which is a tumor blood flow inhibitor, and arrive at the combination of two agents of the claimed invention.

Applicants respectfully submit that citation of Emtage et al. is contradictory to the statements made by the Office in the previous Office Actions. In the Office Action dated April 28, 2008, the Office cited Olsson et al. that apparently teach that human IL-2 is induced by CD80 (B7.1, a CAM molecule). The Office alleged that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to replace the IL-2 with its stimulator (CAM) and a specific analog of XAA, DMXAA with a expected result." See page 4 of the Office Action dated April 28, 2008. Therefore, according to the Office, IL-2 is replaceable with B7.1. The citation of Emtage et al. demonstrates that B7.1 and IL-2 are not replaceable as previously alleged by the Office.

In the absence of any suggestion or motivation in either of the cited references, the skilled artisan will not be motivated to replace the adenoviral expression vector expressing IL-2 of Emtage et al. with DMXAA of Wilson et al. and administer DNA encoding B7.1 prior to DMXAA, as in the claimed invention.

No reasonable expectation of success

The Office alleges on pages 5-6, transitioning paragraph of the Office Action dated December 22, 2008:

> One of ordinary skill in the art at the time the invention was made would have been motivated with reasonable expectation of success to modify the treatment schedule and the method steps by administering B7.1 prior to the DMXAA and into one or more sites in the tumor in order to optimize and increase the efficacy of the treatment because Emtage et al., have suggested the B7.1 activating T cells, as such, one skilled in the art would have been motivated to give the B7.1 DNA prior to the other antitumor agent that functions immediately in order to let the B7.1 protein expression and activating the T cell first.

The Office has not made out a *prima facie* case that the administration of DNA encoding B7.1 prior to administering DMXAA would have been obvious based on teachings of Emtage et al., Wilson et al., or Lash et al. This showing is necessary in support of a *prima facie* case of obviousness.

In *Ex parte Whalen II*, __ Westlaw __ (PTO Bd. App. & Int. 2008) (precedential) (Grimes, APJ) (copy attached as **Exhibit I**), an expanded panel of the Board, including Chief APJ Fleming, stated that (*see* page 14):

> "[h]ere, the Examiner has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that those skilled in the art would have considered it obvious to 'optimize' the prior art compositions by increasing their viscosity to the level recited in the claims."

Ex Parte Whalen II, supra., cited on page 14:

> "While 'the discovery of an optimum value of a variable in a known process is normally obvious,' *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977), this is not always the case. One exception to the rule is where the parameter optimized was not recognized in the prior art as one that would affect the results.
>
> *Id.*

The Office has not pointed to any teaching in the cited references to support the conclusion that those skilled in the art would have considered it obvious to "optimize" the cited references by administering DNA encoding B7.1 prior to administering DMXAA, as recited in the claims. On the contrary, Emtage et al. teach concurrent administration of B7-1 and IL-2 and Lash et al. teach simultaneous administration of DMXAA and 5-HT (see, e.g., Table 1, page 442 of Lash et al.).

Meanwhile, the instant specification shows[1] surprising results that combined therapy by timed delivery of B7.1 and DMXAA eradicates large tumors:

> ... established tumours (0.6-0.8 cm in diameter) were first treated with B7.1 to stimulate anti-tumour immunity, and DMXAA and FAA were administered one day later to retard tumour growth. Remarkably, tumours rapidly diminished in response to the combination of B7.1 and DMXAA accompanied by massive necrosis, such that by the third week of treatment tumours had completely disappeared (FIG. 1b).

Thus, not only has the Office failed to present a *prima facie* case of obviousness, Applicants' evidence of record rebuts any *prima facie* case, had one been presented.

In light of the above-noted evidence of record as presented above, Applicants request the Office to withdraw this rejection under 35 U.S.C. §103(a).

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

[1] See page 16, lines 25-34 to page 17, lines 1-7 of the application as filed.

III. CONCLUSION

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date March 23, 2009

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